Stimulation of histone deacetylase activity by metabolites of intermediary metabolism.

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Public Summary:
Histones are proteins around which DNA wraps to form chromatin, the physiological form of the genome. Histones are dynamically modified by small chemical groups such as acetylation. HDACs are a class of enzymes that remove the acetyl groups from histones and function in a variety of cellular processes such as gene expression, contributing to cellular identity such as embryonic stemness or malignant states. Inhibition of HDACs has many cellular consequences depending on the context. For instance, HDAC inhibition can help with generation of induced pluripotent cells or arrest growth of cancer cells. In fact, HDAC inhibitors are being pursued as a form of anti-cancer therapy with more than 80 clinical trials underway. Therefore it is important to understand how HDACs normally function in the cell. In this paper, we discovered a series of natural metabolites that normally stimulate the activity of HDAC proteins. We characterized this stimulation in biochemical detail. Our findings shine light on why a certain chemical molecule functions as an HDAC inhibitor (because it is similar to a natural metabolite) and thus may help with development of more effective drugs to inhibit HDACs.

Scientific Abstract:
Histone deacetylases (HDACs) function in a wide range of molecular processes, including gene expression, and are of significant interest as therapeutic targets. Although their native complexes, subcellular localization, and recruitment mechanisms to chromatin have been extensively studied, much less is known about whether the enzymatic activity of non-sirtuin HDACs can be regulated by natural metabolites. Here, we show that several coenzyme A (CoA) derivatives, such as acetyl-CoA, butyryl-CoA, HMG-CoA, and malonyl-CoA, as well as NADPH but not NADP(+), NADH, or NAD(+), act as allosteric activators of recombinant HDAC1 and HDAC2 in vitro following a mixed activation kinetic. In contrast, free CoA, like unconjugated butyrate, inhibits HDAC activity in vitro. Analysis of a large number of engineered HDAC1 mutants suggests that the HDAC activity can potentially be decoupled from "activatability" by the CoA derivatives. In vivo, pharmacological inhibition of glucose-6-phosphate dehydrogenase (G6PD) to decrease NADPH levels led to significant increases in global levels of histone H3 and H4 acetylation. The similarity in structures of the identified metabolites and the exquisite selectivity of NADPH over NADP(+), NADH, and NAD(+) as an HDAC activator reveal a previously unrecognized biochemical feature of the HDAC proteins with important consequences for regulation of histone acetylation as well as the development of more specific and potent HDAC inhibitors.